REMARKS

Claims 1, 7 - 10, 12 and 14 - 20 are now pending in the application. Claims 1, 8, 12, 15 and 17 were previously amended. Claims 1 and 7 are currently amended. Claims 2-6 and 13 were previously canceled. Claim 11 is currently canceled. Claims 9, 10, 14, 16, 18 and 19 are original. Claim 20 is new. A copy of the claims now pending in the application showing changes made to currently amended claims in accord with 37 CFR 1.121, as revised, has been provided.

No new matter has been introduced by virtue of the amendments made herein. Accordingly, applicants respectfully request their entry. In view of the amendments made herein and the remarks below, applicants respectfully request reconsideration and withdrawal of the rejection set forth in the February 26, 2003 office action.

Rejection under 35 USC § 103(a)

The Examiner rejected claims 1, 7 - 12 and 14 -19 under 35 USC § 103(a) as unpatentable over Doogan et al. (U.S. 4,962,128) in view of Howard et al. (U.S. 5,597,826).

The applicants have amended claim 1 to recite:

> "A pharmaceutical composition which comprises:
>
> an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride for oral administration comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride and pharmaceutically acceptable excipients; wherein the excipients are ethanol and glycerin in an amount of about 8 to about 50% ethanol by weight in glycerin."

Support for the term "solution" can be found on page 6, line 29, of the instant specification. Support for the term "filterable" can be found on page 9, line 19, where it is stated "The compounded solution is passed through a filter ..." and on page 10, Example 1, line 10. Support for the sertraline hydrochloride range "about 18 mg/ml to about 78 mg/ml" can be found in Example 5, page 10, line 26, to page 11, line 5, where a wider range is given and at page 7, line 10, where a wider range is also given. Support for the ethanol range of "about 8 to about 50%" can be found on page 7, line 25, of the instant specification.

The Examiner cites Doogan, col. 1, line 68, which recites the hydrochloric acid salt of sertraline and col. 2, lines 20 –23, which recites dosages that range from about "...50 - 500 mg per day when used to treat obsessive-compulsive disorder and from about 25-500 mg per day when used to treat other anxiety-related disorders...". The Examiner also cites Doogan at col. 2, line 65, to col. 3, line 2, which beginning at line col. 2, line 63, recites in full: "When *aqueous* [emphasis added] suspensions and/or elixirs are desired for oral administration, the sertraline, or pharmaceutically acceptable salt thereof, may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and various like combinations thereof."

Applicants respectfully submit that the above cited reference teaches diluents such as ethanol and glycerin within "...aqueous suspensions and/or elixirs ..." Applicants respectfully refer the Examiner to Dorland's Illustrated Medical Dictionary, 25th edition, (W. B. Saunders) which at page 125 defines the term "aqueous" as "watery; prepared with water." Applicants further respectfully note that those skilled in the art will recognize that when the term "aqueous" is used to describe a liquid preparation, the liquid in the preparation is primarily water. Therefore, Doogan's recital of ethanol and glycerin are within the context of diluents used with a liquid preparation wherein the liquid is primarily water.

The Examiner cites Howard et al., col. 20, line 31, which recites "[s]ertraline hydrochloride..." and medicinal uses thereof, and to support a dose of sertraline hydrochloride of "from 0.1 to 200 mg" the Examiner cites this reference at col. 24, lines 7 – 8, which is a portion of the paragraph at col. 24 lines 3 – 9, which recites:

> "A proposed dose of the compounds of formula I in the combination formulation for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., migraine) is from about 0.01 mg. to about 2000 mg., preferably from about 0.1 mg. to about 200 mg of the active ingredient of formula I per unit dose which could be administered, for example, 1 to 4 times per day."

Applicant respectfully notes that the above paragraph makes no reference to sertraline and that the compounds of formula I are distinct from sertraline. However, at col. 24,

lines 10 – 17, Howard et al. recite: "A proposed dose of a 5-HT uptake inhibitor, preferably sertraline, *in the combination formulation* [emphasis added] for oral, ... administration .... is from about 0.1 mg to about 200 mg of the 5-HT re-uptake inhibitor per unit dose...." Applicants submit that the teaching here is the dosage of a 5-HT uptake inhibitor, preferably sertraline, *in the combination formulation,* not of sertraline itself. Applicants also submit that there is no teaching or suggestion that would lead an investigator seeking "an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride" to the concentration range of "about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride" recited for the pharmaceutical composition of claim 1, as currently amended.

The Examiner also cites Howard at col. 22, lines 51 – 56, which beginning at col. 22, line 47, and continuing to line 57, recites:

> "Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid)."

In addition, the Examiner cites col. 23, lines 56 – 58, which recites "Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly for such purposes."

The applicants again note the oral pharmaceutical formulation referred to in the foregoing is a combination of a compound of formula I with a 5-HT re-uptake inhibitor, preferably sertraline (see col. 23, lines 41 - 43). Applicants submit that the presence of another complex chemical species in Howard's pharmaceutical composition is a disincentive to the skilled artisan seeking guidance in the preparation of "an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride" as this

introduces complications regarding the solubility of sertraline hydrochloride. Applicants submit that there is therefore no motivation to combine Howard with Doogan.

Applicants further respectfully submit that even if Howard et al. were combined with Doogan, the combination would not arrive at the pharmaceutical composition of claim 1, as currently amended. Howard et al. recite "...non-aqueous *vehicles* (e.g. almond oil, oily esters or ethyl alcohol)..." and do not teach or suggest the use of glycerin as a non-aqueous vehicle, let alone the combination of glycerin with ethanol as a non-aqueous vehicle. Applicants further submit that the combined references do not teach or suggest the pharmaceutical preparation of currently amended claim 1 which recites "...an essentially nonaqueous, *filterable* liquid concentrate *solution* of sertraline hydrochloride ... comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride and pharmaceutically acceptable excipients; wherein the excipients are ethanol and glycerin".

Applicants submit that at best the combination of Howard with Doogan teaches away from the pharmaceutical preparation of currently amended claim 1 which requires a nonaqueous sertraline chloride solution that is filterable, while Howard recites nonaqueous vehicles as well as suspending agents and emulsifying agents, but not filterable solutions. There is no suggestion in Howard that would lead the skilled artisan to combine the diluents recited in Doogan in the absence of water let alone to combine glycerin and ethanol to produce the filterable sertraline hydrochloride solution recited in currently amended claim 1.

The Examiner states that Johnson (applicants assume this citation refers to EP 0 768 083) "teaches the use of diluents such as ethanol and glycerin". Applicants submit that Johnson states: "When *aqueous* [emphasis added] suspensions and/or elixirs are desired for oral administration, the sertraline, or pharmaceutically acceptable salt thereof, may be combined with various sweetening or flavoring agents, coloring matter or dyes and , if so desired, emulsifying and/or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and various like combinations thereof." Applicants respectfully submit that the above cited reference teaches diluents such as ethanol and glycerin <u>within</u> "...aqueous suspensions and/or elixirs ..." Applicants respectfully again refer the Examiner to Dorland's Illustrated Medical Dictionary which

defines the term "aqueous" as "watery; prepared with water." Applicants further respectfully note that those skilled in the art will recognize that when the term "aqueous" is used to describe a liquid preparation, the liquid in the preparation is primarily water. Therefore, Johnson's recital of ethanol and glycerin are within the context of diluents used with a liquid preparation wherein the liquid is primarily water. Thus, combining Johnson with the cited references does not teach or suggest that water should be excluded, but rather teach its *inclusion*, and would produce a suspension and/or elixir which is primarily water having in addition ethanol and glycerin. Applicants still further submit that Johnson does not teach or suggest an "essentially nonaqueous, liquid concentrate solution of sertraline hydrochloride" as recited by claim 1, as currently amended, and indeed teaches away from an "...essentially nonaqueous, ... solution...." Applicants respectfully submit that Johnson teaches away from claim 1, as currently amended, and the combination of Johnson with the cited references teach away from claim 1, as currently amended, which recites "...an essentially nonaqueous, filterable liquid concentrate solution of sertraline hydrochloride ... comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride and pharmaceutically acceptable excipients; wherein the excipients are ethanol and glycerin in an amount of about 8 to about 50% ethanol by weight in glycerin."

Applicants further submit that the combination of ethanol and glycerin produce the unexpected result of a "...filterable liquid concentrate solution of sertraline hydrochloride comprising about 18 mg/ml to about 78 mg/ml of sertraline hydrochloride.." as recited in currently amended claim 1. Applicants note that the maximum level attained with the combination of ethanol and glycerin is almost 5 times greater than that attained with the use of ethanol alone which produces a maximum sertraline hydrochloride level of only 17 mg/ml (see Example 4, page 10, lines 21 – 25, of the instant specification).

Applicants further submit that the surprising concentration levels attainable with the nonaqueous filterable liquid concentrate solutions of claim 1 have the practical and commercially important consequence of enabling the preparation of a range of dosage levels, including the preferred level of about 22.4 mg/ml of sertraline hydrochloride which is equivalent to about 20 mg/ml of sertraline (see pages 5 and 7 of the instant specification) and is not attainable with ethanol alone.

Applicants submit that claim 1, as currently amended, is patentable under 35 USC § 103(a) over the cited references, either separately or in combination, and respectfully request withdrawal of the rejection.

Applicants have also added new claim 20, dependent on claim 1, that recites a sertraline hydrochloride level of "...about 18 mg/ml to about 30 mg/ml ... and ethanol and glycerin in an amount of about 8 to about 20% ethanol by weight in glycerin" in order to more completely claim the invention.

Original claim 7 has been currently amended to make it dependent on claim 1.

Without prejudice to the applicants' rights, and in the interests of facilitating prosecution, Applicants have canceled original claim 11.

Applicants further submit that currently amended claim 7, claims 8, 9, 10 and new claim 20, all of which incorporate the novel and unobvious features of claim 1, are all patentable under 35 USC § 103(a) over the cited references, either separately or in combination, and respectfully request withdrawal of the rejection.

Applicants also submit that claims 12 and 14 -19 which incorporate the novel and unobvious features of the pharmaceutical composition of claim 1 are all patentable under 35 USC § 103(a) over the cited references, either separately or in combination, and respectfully request withdrawal of the rejection.

In view of the amendments set forth herein and remarks above, Applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§1.16 and 1.17 or to credit any overpayment to Deposit Account No. 16-1445.

Date: May 29, 2003

A. David Joran
Attorney for Applicant(s)
Reg. No. 37,858

Pfizer Inc
Patent Department
150 East 42nd Street – 5th Floor
New York, NY 10017-5755
(212) 733-3381